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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,563	05/02/2002	Dan L. Eaton	P3230R1C001-168	9765

9157 7590 12/17/2004

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,563	EATON ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2004/2002*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendments filed 5-8-02 and 9-9-02 have been entered into the record.

The response, amendment, information disclosure statement, inventors declarations filed under 37 CFR § 1.132, Exhibits 1-8 filed October 4, 2004 have been entered into the record. It is noted that Exhibits I and II are declarations pursuant to 37 C.F.R § 1.132 executed by J. Christopher Grimaldi. Exhibits III and VII are declarations pursuant to 37 C.F.R § 1.132 executed by Paul Polakis, PhD. and Avi Ashkenazi Ph.D. respectively. Claims 1-8 and 11-13 are pending and under examination. Claims 9-10 having been cancelled.

The text of Title 35 of the US Code not cited herein is of record in the first office action on the merits mailed 7-1-04.

Correction of Inventorship

Pursuant to the request under 37 C.F.R. §1.48(b) signed by a party set forth in §1.33(b) and the filing of the processing fee set forth in § 1.17(i), the following individuals have been removed as inventors: Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen and Colin K. Watanabe.

Objections/Rejections Withdrawn

The objection to the claims pursuant to MPEP 2173.05(s) and not further limiting are withdrawn in view of the amendment to the claims and Applicants' arguments.

The objection to the title is withdrawn in view of Applicants' amendment.

The objection to the specification for the use of the trademarks TWEEN™, PLURONICS™ AND LIFESEQ™ is withdrawn in view of the amendments to the specification.

The objection to the specification as lacking a paper copy of the sequence listing is withdrawn in view of the amendment to the specification to include the paper copy of the sequence listing.

The rejection of the claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants' amendments to the claims.

Rejections Maintained

Priority

Applicants argue that the nucleic acids have credible, specific and substantial utility and that they are entitled to the priority date of 6-24-98 of provisional document 60/090,444. The provisional document does not provide written description of the claims as now set forth for reasons made of record and only describes SEQ ID NO:56. The provisional document fails to establish utility and enablement for the now claimed polypeptides in any of the priority documents for reasons made of record herein. Description of the protein of SEQ ID NO:56 in the provisional application does not provide compliance with 35 USC § 120 for reasons set forth in the previous office action of record and reasons set forth herein. Applicants are not granted priority for the provisional document 60/090,444.

Applicants argue that the data in Example 18 (tumor versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8-24-00 on page 93, line 3, through page 96, line 35. This is not persuasive, the priority document does not comply with 35 USC § 120, written description, utility and enablement for reasons set forth in the previous office action of record and reasons set forth herein. This relied upon utility is not a substantial utility for reasons made of record and argued herein.

The priority date is the instant filing date of 5-2-02.

Information Disclosure Statement

The information disclosure statement filed 9-10-02 has been considered, an initialled copy is enclosed. It is noted that the issue date and inventor of submitted patent number 5,546,637 has been corrected in this IDS. The information disclosure statement filed 10-4-04 has not been fully considered. The NEW patent has not been considered because the information disclosure statement lacks the requisite fee. The remaining refereces are duplicative to the ones filed on 9-10-02 and have been lined through.

Rejections Maintained

Claims 1-8 and 11-13 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility is maintained.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that the requirement for a substantial utility defines a "real world use" and cite *Brenner v Manson*, 383 US 559,534(1996) already of record. Applicants argue that MPEP 2107.01 that states that office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulation to mean that products or services based on the claimed invention must be "currently" available to the public. This is not persuasive, the rejection set forth did not require "current public availability", but a specific and substantial utility for the now claimed invention. Applicants argue that any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial utility". This is not persuasive, the relied upon utility (decreased protein expression in melanoma as compared to normal skin) specifically requires or

constitutes carrying out further research to identify or reasonably confirm a "real world" context of use and as such is therefore not a "substantial utility" (see MPEP 2107.01(1)). Applicants argue that the USPTO must establish that it is more likely than not that one of skill the art would doubt the truth of the statement of utility, namely that the gene encoding PRO1027 is differentially expressed in certain cancers compared to normal tissue and useful as a diagnostic tool. The argument has been fully considered, but is not persuasive. Utility requires that the skilled artisan be able to use the claimed invention. The specification does not provide a specific and substantial or a well-established use. Applicants have provided a single analysis of nucleic acid without any relative range for basing a utility of under-expression for the claimed protein(s). There is no guidance on how to use this information. No levels (relative or absolute) are disclosed. Applicants argue that if the gene is differentially expressed in cancer versus non-cancer tissue, then its mRNA and encoded polypeptide are useful as diagnostics. This argument is pertinent to the instant claims because of the functional limitation added wherein the nucleic acid encodes a polypeptide that is more highly expressed in normal skin tissue compared to melanoma. The argument has been fully considered, but is not persuasive for reasons made of record herein. Further, if one cannot use the encoding nucleic acid as a diagnostic tool for tumors, then one cannot use the encoded polypeptide either. There is no data regarding protein expression in melanoma and normal skin in the specification and Applicants are attempting to rely upon a correlation of increased mRNA levels of SEQ ID NO:55 with increased protein levels (SEQ ID NO:56). The art clearly establishes that DNA copy number, mRNA levels and protein levels are not inexorably related, in that an increase in one necessarily leads to an increase in all of them. Transcription levels (mRNA) do not correlate with polypeptide levels and Applicants have not provided any specific role for the lack of the claimed polypeptide in cancer or identified its biological function. Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation

between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances that varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Further, the concept that transcription levels do not correlate with protein levels was so well known to the art that it was presented in a text book Lewin, Genes VI (1997) Chapter 29, pages 847-848 which specifically teaches "... production of RNA cannot be inevitably be equated with production of protein...." (page 487, column 2, last paragraph). This concept reconfirmed by a variety of studies such as that evidenced by Gokman-Polar et al (Cancer Research 61:1375-1381, 2001) that indicates the absence of any necessary correlation between increased mRNA levels and increased protein levels. Gokman-Polar et al that teach "Quantitative reverse transcription-PCR analysis revealed that the PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isoenzyme expression is likely regulated at the posttranscriptional/translational level" (see abstract). Gokman-Polar et al show in Figure 6-7 that there is no increasing mRNA expression for any of the isoenzymes, while the protein is significantly overexpressed as shown by Figure 4-5. Further, Pennica et al (PNAS, 95:14717-22, 1998) establishes that there is a lack of correlation between gene amplification and protein expression of the WISP protein and this teaching in combination with Haynes et al indicates that there is no significant correlation between nucleic acid level and translation indicates that the asserted correlation between each gene, mRNA and corresponding protein in tumors is unpredictable and well known to the skilled artisan. Applicants have presented no showing that the amount of both the mRNA(gene) and protein are increased as compared to normal cells for PRO1027. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of

a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). This specification does not teach the expression level of the claimed protein, nor is it demonstrated scientifically significant and is therefore at best a preliminary observation that requires substantive experimentation to ascertain the veracity thereof. Therefore, the art indicates that it is not the norm that increased/decreased gene transcription results in increased/decreased polypeptide levels and the asserted utility of the PRO1027 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. The need for further research to reasonably identify or confirm a utility is not "substantial" because it does not identify a "real world" utility (MPEP 2107.01(1)). Even if the nucleic acid has a utility as a melanoma tumor marker (a point that the examiner does not conceede) , the encoded protein does not have utility because it is not known what the protein does or if the level of the PRO1027 protein in melanoma corresponds to transcript level (i.e. if an increased amount of transcript corresponds to an increased amount of expressed protein) for reasons made of record. It does not necessarily follow that an increase in transcript levels results in a corresponding increase in protein expression, such that the polypeptide would be useful diagnostically or as a target for cancer drug development. These references establish that one skilled in the art would not associate DNA copy number, mRNA and protein levels and necessarily reflecting each other. Applicants argue that the utility is credible. It is noted that credibility for the asserted utility for the PRO1027 polypeptides as claimed has not be assessed because the relied upon utility is not deemed substantial for reasons of record.

The utility now asserted and relied upon for the claimed polypeptide is *overexpression* of the polypeptide in melanoma with respect to normal skin and that this

differential expression provides for a specific, substantial, and credible utility. This is not persuasive, Applicants have not shown that the polypeptide as shown in SEQ ID NO:56 or any claimed variant or fragment thereof is underexpressed as compared to normal skin. Applicants argue that as provided in Example 18 of the application, the nucleic acid of SEQ ID NO:55 is overexpressed in melanoma relative to normal skin and that this differential expression provides a specific, substantial and credible utility for the now claimed polypeptide.

Applicants rely upon the Grimaldi declarations submitted as Exhibits 1 and 2 to post facto attempt to establish that the nucleic acid in normal skin is significantly higher than that in melanoma. These declarations are not persuasive on their face because they do not address the claimed invention, PRO1027 polypeptide. These declarations are also not persuasive for the following reasons. As to the first declaration of Dr. Grimaldi, Declarant Grimaldi merely reiterates the assertion in the specification that since the RNA levels are different then "this indicates that the gene and its corresponding polypeptide and antibodies are useful for diagnostic purposes to screen samples to differentiate between normal and tumor." This is not persuasive, the assertion relies upon a tight correlation of RNA production with protein expression. The art, as set forth *supra*, clearly recognizes that RNA production does not correlate with protein expression. Declarant asserts at paragraph 6, that the expression levels in the tumor and normal vary by two fold based on a visual quantification using ethidium bromide staining of PCR products on agarose gels. This is not persuasive, visual detection is highly subjective and was graded as + or – or +/- and not is quantitative. Applicants have not set forth the evidentiary basis for their assumption that a visual difference relates to an at least 2-fold difference in cDNA or 2 fold difference in protein. Applicants have provided no objective evidence that supports this assertion of qualitative and quantitative results. With respect to the pooled samples, Declarant says, "That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples

from normal tissues are compared with pooled samples from tumors in the same tissue type," [paragraph 5] without knowing the range of variation there is insufficient guidance. If a clinician took a skin tissue sample from a patient with suspected melanoma, what is the likelihood that when compared with normal tissue, the level of nucleic acid of SEQ ID NO:55 from the patient would be lower? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? Furhter, this appears to be the opinion of Declarant because it is not supported by objective evidence set forth before the examiner. While the 6th paragraph of the first Grimaldi Declaration says that the detection technique used in the specification makes it "reasonable to assume that any detectable differences seen between two samples will represent at least a two-fold difference in cDNA," that statement still does not answer the questions raised above and does not place a specific and substantial use of the nucleic acid or polypeptide encoded thereby in the skilled artisan's hand. The statement that the relative difference in expression is what is important is generally true, but without more specifics about necessary sample size, expression level range for normal and tumor tissues that can used, and other questions, the specification has not provided the invention in a form readily usable by the skilled such that significant further experimentation was unnecessary.

The second declaration by Dr. Grimaldi (Exhibit 2) has been fully considered but is not deemed persuasive. Applicants argue the second declaration of Dr. Grimaldi (Exhibit 2) that states that "in the vast majority of cases, when a gene is over-expressed , as evidenced by an increased production of mRNA, the gene product or polypeptide will also be over-expressed and that the detection of increased/decreased mRNA expression is expected to result in increased/decreased polypeptide expression. At paragraph 4, Declarant discusses mutations of Her2/Neu, and chromosomal translocations that are known to be associated with cancer, and states the "When the chromosomal aberration results in the aberrant expression of mRNA and the corresponding gene product (the

polypeptide) , as it does in the aforementioned cases, the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach.". This argument has been fully considered but is not persuasive because it evinces that the instant specification provides a mere invention to experiment, and not a readily available utility. The PRO1027 gene, unlike Her2/Neu, has not been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t(5;14), no translocation of PRO1027 is known or established to occur. All that the specification demonstrates that the PRO1027 mRNA under-expressed in melanoma as compared to a normal skin control without any statistical analysis, the relevance of a single point is unreliable. No mutation or translocation of PRO1027 has been associated with melanoma. It is not known what whether PRO1027 polypeptide is expressed in melanoma and normal skin and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1027 is decreased in a sample, and invite the skilled artisan to determine the rest of the story. Such is insufficient to meet the requirements of 35 U.S.C. § 101 for the instantly claimed protein. At paragraph 5, Declarant argues that increased mRNA expression is expected to be associated with increased protein production. This argument has been fully considered but is not deemed persuasive because (a) this appears to be Declarant's opinion, and is not supported by fact or evidence (b) there has been no distinction on the record in general or in the specification as filed between total nucleic acid, which includes chromosomal DNA and mRNA. One cannot determine for the data in the specification whether the observed "increase" is due to mutation, copy number differences or transcription rates. It remains that there is no information on the record as to whether the claimed protein is expressed at all in normal tissue, cancerous or otherwise and whether the expression levels correlate with the actual protein levels. It remains that, as evidenced by Pennica et al, Haynes et al, Gokman-Polar et al and Lwein, the issue is simply not predictable, and the specification presents a mere

invitation to experiment. This is further borne out by Declarant's paragraph 6, which proposes further experimentation, should Applicants assertions be erroneous and there is no direct correlation between gene expression and protein expression.

Applicants also present a declaration by Dr. Polakis and referenced in the response as Exhibit 3. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor makers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma that in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes reports of instances where such a correlation does not exist, as exceptions to the rule. This has been full considered but is not found to be persuasive. The declaration does not provide data such that the examiner can independently draw conclusions, or provide any objective evidence with respect to the instantly claimed polypeptides. Only, Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide and the examiner has presented evidence that one of skill in the art would not believe this to be true. Further, while the declaration may allege (no evidence is presented) that there is a correlation between mRNA expression and protein over-expression in some cases, Applicants have presented no objective evidence that the PRO1027 polypeptide is over-expressed as asserted, relative to normal cells. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and

cancerous tissue. For example, Hu et al (Journal of Proteome Research 2:405-412, 2002) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (page 408, middle of right column). Hu et al discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicants argue additional references to support the position that gene levels correlated with levels of mRNA expression and levels of protein expression (Orntoft et al, Hyman et al and Pollack et al; Exhibits 4-6). Applicants characterize Orntoft et al as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicants characterize Hyman et al a providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicants characterize Pollack et al as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. The arguments related to these references have been fully considered but are not persuasive. Orntoft et al appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region (see for example page 44, column 1, last paragraph). Their approach to investigating gene copy number was term CGH. Orntoft et al do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding mRNA levels, from an unknown number of genes, which may or may not be in a chromosomal region that is highly amplified. Orntoft et al concentrated on regions of chromosome with strong gains of chromosomal material containing clusters of genes (page 40). This analysis was not done for PRO1027 in the

instant specification. That is, it is not clear whether or not PRO1027 is in a gene cluster in a region of the chromosome that is highly amplified. Therefore, the relevance of Orntoft et al is not clear. Hyman et al used the same CGH approach in their research. Less than half (44%) of the highly amplified genes showed mRNA over expression (see abstract). Polypeptide levels were not investigated and therefore do not speak to the relationship between mRNA levels and polypeptide levels, which is the issue here. Therefore, the relevance of Hyman et al as it relates to the issue of correspondence of levels of mRNA with levels of polypeptide expression is not clear and Hyman et al does not support utility of the claimed polypeptides. Pollack et al also used CGH technology, concentration in large chromosome regions showing high amplification (page 12,965). Pollack et al also did not investigate polypeptide levels and therefore does not speak to the issue of the correlation of levels of mRNA and encoded polypeptide. Pollack et al also noted contradictory results found by another research group, noting that , "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (page 12,968 end of first paragraph). This leads again to the issue of unpredictability. Therefore, Pollack et al also does not support the asserted utility of the claimed invention. Importantly, none of the later papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO1027 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicants argue that even assuming *arguendo* that there is no correlation between gene expression and protein expression for PRO1027, a polypeptide that is underexpressed or overexpressed in some undefined cancer is still useful and present Exhibit 7, a declaration filed by Dr. Ashkenazi. Dr. Ashkenazi declares that the absence

of gene product over-expression still provides significant information for cancer diagnosis because it enables more accurate tumor classification and hence better determination of suitable therapy. This is not persuasive, there is no evidence that clinicians use information about a gene product NOT being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene product. The specification does not teach how the PRO1027 relates to tumor classification using any clinically relevant standards (i.e. invasive potential, drug resistance, primary or secondary tumor) upon which oncologists (i.e. the skilled artisan in cancer treatment) rely to make therapeutic decisions. Neither, the specification nor the art indicates or contemplates how the claimed PRO1027 polypeptide under or over-expression fits into the alleged tumor classification or to any tumor classification for that matter. Applicants allege that the information of PRO1027 expression or under-expression leads to better determination of a suitable therapy. This is not persuasive, the biological role of PRO1027 in cancer, if any, is not set forth in the specification and it is not clear how the specification leads a clinical to a "better determination of suitable therapy" as asserted by Applicants. This is a hypothetical utility that is not disclosed in the specification. The specification does not disclose the function of PRO1027 as it relates to cancer prevention/promotion and therefore it is not readily apparent to the skilled artisan how to apply any level determination of any disclosed polypeptide with any of the plethora of cancer therapies available to the clinician oncologist (i.e. the skilled artisan in cancer therapy). The function (estrogen receptor) and relationship of Her/Neu2 is clearly established in breast cancer. This function and relationship is not established in the specification for PRO1027 as it relates to melanoma or normal skin cells or any other cell in the art. As such, the polypeptide does not have a well established or substantial utility for the claimed polypeptides.

Applicants argue that the utility of the PRO1027 polypeptide is further supported by the teachings in the article by Hanna et al, submitted as Exhibit 8. Hanna et al does not discuss protein levels, but correlates cancer prospects with amplification of certain

genes. As such, Hanna et al is not dispositive of the central issue herein, the correlation of gene levels, mRNA levels and protein levels.

Since the claims are directed to the PRO1027 polypeptide, it was imperative to find evidence in the relevant scientific literate whether or not a small increase in DNA copy number or mRNA levels would be considered by the skilled artisan to be predictive of increased mRNA and subsequence encoded protein levels. Pennica et al was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Further, Konopka et al (PNAS, 83:4049-56, 1986) states that "Protein expression is not related to amplification of the *abl* gene but to variation in the level of bcr-abl mRNA production from a single Ph1 template" (see abstract). Konopka et al also provide evidence that showing lack of correlation between gene amplification and increased polypeptide level. Gokman-Polar et al and Lewin were cited to teach the lack of correlation between mRNA levels and protein levels was so well established in the art it was cited in a textbook and experimentally exemplified by Gokman-Polar et al. Finally, it is noted that the literature of record cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissues. Haynes et al was cited to provide evidence that polypeptides levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (page 1863). Given even the asserted "visible 2-fold increase in mRNA" (Declaration Dr. Grimaldi as Exhibit 1), and in the evidence presented by Haynes et al, Gokman-Polar et al and Lewin, it is clear that one skilled in the art would not assume that a small increase/decrease in mRNA would correlate with corresponding changes in polypeptide levels. Given the evidence provided by Haynes, Pennica et al and Konopka et al it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA levels or encoded polypeptide levels. In view of the totality of the evidence of record, one skilled in the art would not assume that gene expression necessarily parallels or is predictive of protein expression or

that gene copy number (and would have to perform further experimentation to verify or rule it out. As such, this further experimentation indicates that the asserted utility is not "substantial".

The rejection is maintained for reasons made of record.

Claim 1-8 and 11-13 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for reasons made of record.

Claims 1-5 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record in the first office action on the merits mailed 7-1-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that the amendment of the claims to recite the functional limitation of "wherein the isolated nucleic acid is more highly expressed in melanoma relative to normal skin cells or wherein said isolated nucleic acid encodes a polypeptide that is more highly expressed in melanoma relative to normal skin cells" provide for sufficient distinguishing identifying characteristics of the genus. This is not persuasive, this is not the function of a protein and does not impart specific structural requirements for possession of nucleic acids as set forth in the previous office action of record. The specification does not provide complete or partial structure of a representative number of nucleic acids that encode proteins. There is no known or disclosed function of the protein per se, that would

allow the skilled artisan to envision the genus or proteins now claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description of a genus is more than a mere statement that it is part of the invention and reference to a potential methods of isolating it. The compound itself is required. The specification teaches a single nucleic acid SEQ ID NO:55 that allegedly meets the limitation of "is more highly expressed in melanoma relative to normal skin cells". The specification does not teach that the polypeptide *per se* is more highly expressed, nor does it teach the function of the protein either in normal or cancer cells. The specification does not teach variants of either the nucleic acid or polypeptide. There are no other nucleic acids or polypeptides in the specification as originally filed that fall within the claimed genus. As such, the skilled artisan would not be able to readily envision the claimed genus. The claimed invention as a whole is not described wherein an invention is described solely in terms of methods of making coupled when there is no described or art recognized correlation or relationship between the structure of the invention and the biological function of the molecule. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between the biological function and the structure of the sequence is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. *In re Bell* F.2d 781, 26 USPQ2d (Fed. Cir. 1993). Applicants describe a single protein sequence that falls within the claimed genus. A single polypeptide is not representative of the vast genus now claimed and neither the specification nor the art provide a correlation between the structure of the polypeptide and the property of "more highly expressed in normal skin tissue as compared to melanoma". A patent specification must describe the claimed invention in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention see *Moba,*

B.V. v. Diamond Automation, Inc. 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 116. Applicants have not pointed to support for the now claimed variants or even identified which polypeptides, other than the claimed polypeptide set forth in SEQ ID NO:56, as set forth in the specification as filed function as instantly claimed. A single polypeptide does not describe the genus of polypeptides that have the recited property as claimed. There is no conception of other polypeptides that fall within the genus to establish that, Applicants were in possession of the now claimed genus at the time of filing. The now recited property does not describe possession of additional polypeptides having the recited sequence at the time of filing. Thus, it is clear that the specification as filed does not isolate or describe multiple polypeptides having the property as claimed. As such, the claims fail to satisfy the written description requirement. One skilled in the art could not envision the genus, because the specification lacks a description of the correlation of the structure of a representative number of polypeptides with the now recited function of the genus. Possession my be shown in a variety of way including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structures. Applicants have not isolated a number of polypeptides within the genus that have the property and do not disclose the function of the polypeptide pre se therefore does not reduce to practice the genus and does not provide a correlation of the claimed structure with the claimed property. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed. See for example *Fujikawa v Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of the a genus because it would not "reasonably lead" those skilled in the art to any particular species. In the instant case, while the skilled artisan may envision may changes to the polypeptide of SEQ ID NO:56, one can not envision what changes to the

structure or what part of the structure of SEQ ID NO:56 are conserved as it correlates with the now claimed property. The specification provides no guidance and does not set forth a representative number of polypeptides with the claimed property to allow the skilled artisan to envision the genus and the distinguishing identifying characteristics of the now claimed genus.

The rejection is maintained.

Claims 1-7, 11 and 12 stand rejected under 35 U.S.C. 102(b) as being clearly anticiapted by Rhodes et al, (Database sequence, publically available May 1, 1999) is maintained for reasons made of record for claims 1-11 in the office action mailed 7-1-04.

Applicants arguments have been considered but are not persuasive. Applicants argue their priority date. The priority date has not been granted for reasons made of record. None of the priority documents have written description, enablement and utility as required by 35 USC 120 and 119(e) to be accorded the earlier filing date for the now claimed invention. Further, Applicants assert that since the date of the earliest reference preceeds Rhodes, then Applicants have shown possession of the invention before the critical date and can do so via the "Stempel Doctrine" and do not have to file a declaration persuant to 37 CFR 1.131. This is not persuasive, Applicants are not entitled to priority to the provisional document nor any other claimed priority document for the reasons made of record *supra* and in the previous office action of record. Further, the relied upon utility, increased mRNA expression in melanoma as compared to normal skin tissue, was not even disclosed until PCT/US00/23328 filed 8-24-2000. Even if this utility was substantial (which it is not for reasons made of record) the cited reference would still be a 102(b). A 102(b) reference is a "statuatory bar", for which neither the "Stempel Doctrine" nor a declaration persuant to 37 CFR 1.131 can overcome.

The rejection is maintained

New Grounds of Objection/Rejection

The use of the trademarks have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

The trademark American Type Culture Collection (ATCC ™) needs to be recognized wherever it appears.

Claims 1-6 and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification at pages 120-123 lacks complete deposit information for the deposit of the full length cDNA encoding the claimed polypeptide deposited at the American Type Culture Collection as set forth in embodiment (e) of claims 1-6 and 11-13. The referral to the deposit on page 123 is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 have been met. The specification states that pursuant to an "agreement" between Genentech, Inc. and the ATCC™, permanent unrestricted availability to the public of the progeny of the culture upon issuance of "the pertinent US Patent" is provided for. This is insufficient because agreements are contracts that are revocable and the conditions therein are revocable. Further, it is unclear what would be considered the "pertinent US Patent". As such, Applicants are required to provide assurances that All restrictions upon pubic access to the ATCC™ accession number 203245 as specifically claimed, will be "irrevocably removed upon the grant of a patent from this application" specifically using this exact language. Since "agreements" are subject to revocation, this assurance is required for patent

purposes. The assurances should be made by an affidavit or declaration by Applicants or Assignees or a statement by an attorney of record that has authority and control over conditions of the deposit over his or her signature and registration number. Applicants are specifically directed to MPEP 2424.01 that states "with one possible exception (37 CFR 1.808(b)), that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent" are required see *Ex parte Hildebrand*, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990.

Status of the Claims

All claims stand rejected.

Conclusion

This action is non-final in view of the new grounds of rejection and lines of argument set forth herein were not specifically set forth in the first office action on the merits.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645